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TENG, S	
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1 - 39 are pending in the application.
   Of the above, claims 6 - 8 and 15 - 39 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1 - 5 and 9 - 14 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 1 - 39 are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Response
DOCKETED
FOR 9-7-94
BY _____
CHEC'D BY _____

REC'D - A.W.D.
JUN 10 1994
DOCKET DESK

EXAMINER'S ACTION P19794
COMPUTER INPUT #

PTOL-326 (Rev. 2/93)

1. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-5 and 9-14, drawn to a polynucleotide encoding kappa opioid receptor, classified in Class 435, subclass 69.1 and Class 536, subclass 23.1.

II. Claims 6-8, drawn to a kappa opioid receptor, classified in Class 530, subclass 395.

III. Claims 15, 16, and 18-21, drawn to antibodies and immunoassays, classified in Class 435, subclass 7.1 and Class 530, subclass 388.1.

IV. Claim 17, drawn to a method for detecting a mRNA encoding kappa opioid receptor, classified in Class 435, subclass 6.

V. Claims 22-27, drawn to polynucleotides encoding variant kappa opioid receptors, classified in Class 435, subclass 172.1.

VI. Claims 28-33, drawn to variant polypeptide receptors, classified in Class 530, subclass 350.

VII. Claims 34-39, drawn to a process for detecting ligands that interact with the variant receptor, classified in Class 435, subclass 7.1.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related because the polynucleotide of Invention I encodes the protein of Invention II. However, they are patentably distinct inventions because the protein of Invention II maybe obtained via materially different processes other than transcription and translation of the isolated polynucleotide of Invention II, such as organic syntheses or isolation from its native source.

Inventions I and III are related because the antibodies of Invention III react with the protein that is encoded by the polynucleotide of Invention I. However, they are patentably distinct inventions because the antibodies can be generated by immunizing animals with the protein isolated from its native source or with synthetic peptides.

Inventions I and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case, the product as claimed can be used in a materially different process such as to produce large quantities of the protein in host cells.

Inventions {I and II} and Inventions {V and VI} are related as receptor and variant receptors and their encoding

polynucleotides. However, they are patentably distinct inventions because the variant polynucleotide and polypeptide can be obtained by synthetic processes. The polynucleotide encoding the variant receptor can be generated by ligating synthetic primers encoding different portions of the variant receptor. The variant receptor can be generated by ligating synthetic peptides.

Inventions I and VII are related because the polynucleotide of Invention I encodes the receptor and the process of Invention VII requires the variant receptor. However, since the method of Invention VII does not require the polynucleotide of a opioid receptor, Inventions I and VII are patentably distinct inventions. The variant receptor can be obtained by synthetic processes.

Inventions II and III are related because the antibodies of Invention III react with the protein of Invention II. However, they are patentably distinct inventions because the antibodies of Invention III can be generated by using synthetic peptides. The protein can be used to screen for ligands.

Inventions II and IV are related because the process of Invention IV requires the polynucleotide that encodes the protein of Invention II. However, they are patentably distinct inventions because the method steps of Invention IV are carried out with the encoding polynucleotide and do not require the protein.

Inventions II and VII are related because the process of Invention VII is a method for detecting ligands that interact with the variant kappa opioid receptor. However, since the required starting material for the process is the variant receptor, Inventions II and VII are patentably distinct inventions. The variant receptor can be obtained by synthetic processes.

Inventions III and IV are related because the polynucleotide required by the process of Invention IV encodes the protein that binds to the antibodies of Invention III. However, they are patentably distinct inventions because the method steps of Invention IV are carried out with the encoding polynucleotide and do not require the antibodies of Invention III.

Invention III and Inventions {V and VI} are related because the antibodies of Invention III bind to the kappa opioid receptor, which is related to the variant receptors of Inventions V and VI. However, since the antibodies can be generated by using a synthetic peptide encoding a portion of the kappa opioid receptor, Invention III and Inventions {V and VI} are patentably distinct inventions.

Inventions III and VII are related because the antibodies of Invention III is specific for the kappa opioid receptor and the process of Invention VII is a method for detecting ligands that interact with the variant kappa opioid receptor. However, since

the method steps of Invention VII do not require anti kappa opioid receptor antibodies, Inventions III and VII are patentably distinct inventions.

Invention IV and Inventions {V and VI} are related because the method of Invention IV detects the mRNA that encodes the kappa opioid receptor. However, since the method of Invention IV is carried out with the polynucleotide encoding the kappa opioid receptor and not the polynucleotide encoding the variant receptor, Invention IV and Inventions {V and VI} are patentably distinct inventions.

Inventions IV and VII are related as processes of using the encoding polynucleotide and the variant receptor polypeptide. However, they are patentably distinct inventions because they require different starting materials and different method steps such that the method steps for each are not required for the other.

Inventions V and VI are related as polynucleotides and polypeptides encoding the variant opioid receptors. However, since the variant receptors can be obtained by synthetic processes and do not need the polynucleotide of Invention V, Inventions V and VI are patentably distinct inventions.

Inventions {V and VI} and Invention VII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the

process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case, the product as claimed can be used in a materially different process. The polypeptide can be used to generate antibodies specific for the variant receptor. The polynucleotide can be used to as probes for northern or southern bloat analyses.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Mr. Daniel Coughlin on April 13, 1994, a provisional election was made with traverse to prosecute the invention of Group I, claims 1-5 and 9-14. Affirmation of this election must be made by applicant in responding to this Office action. Claims 6-8 and 15-39 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Applicants are reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

2. Claims 1, 2, 5, and 9-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, and 9-14 are indefinite because it is not clear whether the polynucleotide encodes a full length or a truncated receptor. The specification defines "the kappa opioid receptor polypeptide" as comprising the amino acid sequence set forth in SEQ ID NO:12, the full length protein, and as comprising less than 400 amino acids, which encompasses truncated peptides (page 25, lines 22-25). The specification defines the "polynucleotide" as comprising 680 to several hundred thousand base pairs which encompasses polynucleotides encoding truncated proteins (page 21, lines 13-19). Claims 1, 9, and 11 should be amended to clarify the claimed invention.

Claim 5 is vague and indefinite because the conditions for hybridization are not specified. Under low stringency conditions, an enormous number of nucleic acid fragments can hybridize to a polynucleotide encoding an opioid receptor.

Claim 14 is incomplete as a method claim because it is missing a method step. The claimed invention is a process for preparing an opioid receptor; however, the process does not recite a step for recovering the receptor.

3. Claims 1, 2, 5, and 9-13 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the polynucleotides encoding the mouse kappa opioid receptor (SEQ ID NO:1) and the human kappa opioid receptor (SEQ ID NO:11). See M.P.E.P. §§ 706.03(n) and 706.03(z).

The specification does not enable all kappa opioid receptor polynucleotides. The specification teaches cloning of the human and mouse receptors having specific polynucleotide sequences, but does not disclose procedure for cloning all kappa opioid receptors from other species. Applicant has provided no evidence that the polynucleotide sequences of the kappa opioid receptors are conserved across species. Consequently, it is unpredictable that kappa opioid receptors from other species can be isolated by methods routinely practiced in the art. Furthermore, proteins from different species are encoded by different amino acid sequences and could possess

different functional activity. Thus, it is not predictable that the kappa opioid receptor polynucleotides from other species encode receptors with the same functional activity as the human or mouse receptor.

Applicant has not characterized the receptor sufficiently to enable the skilled artisan to make and/or use all polynucleotides especially those that encode a portion of the kappa opioid receptor. The specification does not disclose the residues which encode the active site of the protein and does not teach the residues which can be deleted from the sequence without affecting the activity of the protein. In the absence of such information, it would require undue experimentation of the skilled artisan to obtain polynucleotides for making functional peptides. Moreover, the specification does not teach which oligonucleotides are specific for the kappa opioid receptor and can be used as probes for southern and northern blot analyses.

The specification does not adequately teach polynucleotides which are identical or complementary to at least 10 contiguous bases of SEQ ID NO:1 and hybridize to an opioid receptor polynucleotide. First of all, there exist distantly related nucleic acid molecules that are identical to at least 10 contiguous bases of SEQ ID NO: 1, for example, the human platelet glycoprotein IIIa or the human somatostatin receptor gene (see attached sequence comparison). Secondly, as mentioned earlier,

the conditions for hybridization are not specified. Under low stringency conditions, an enormous number of polynucleotides, including distantly related sequences, can hybridize to the polynucleotide encoding an opioid receptor. The specification does not teach how to isolate and/or use each of these distantly related polynucleotides. Furthermore, the specification does not disclose other nucleic acid sequences that hybridize to a polynucleotide encoding an opioid receptor under high stringency conditions. Therefore, it is not evident that such sequences exist or that such sequences are present in sufficient quantities for isolation. Also, it is unpredictable whether such sequences have the same functional activity as the kappa opioid receptor. Thus, in the absence of teaching with respect to the sequences that hybridize to the polynucleotide encoding the opioid receptor, it would require undue experimentation of the skilled artisan to make and/or use the sequences encompassed by the claims.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or

on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 5 is rejected under 35 U.S.C. § 102(a) as being anticipated by Evans et al. Evans et al. teach isolation of the cDNA encoding delta opioid receptor. The disclosed receptor contains several segments that are identical to at least 10 contiguous bases of to SEQ ID NO:1 (see attached sequence comparison). The polynucleotide of Evans et al. would hybridize to the polynucleotide encoding an opioid receptor. Thus, claim 5 is anticipated by Evans et al.

5. Claims 1-5 and 9-13 are rejected under 35 U.S.C. § 102(b) as being anticipated by Xie et al. Xie et al. teach the isolation of the cDNA encoding the human Kappa opioid receptor (abstract and figure 3). Xie et al. also teach expression vectors comprising the isolated cDNA and recombinant production of the receptor (pages 4124 and 4125). In the absence of evidence to the contrary, the claims are anticipated by Xie et al.

6. Claim 5 is rejected under 35 U.S.C. § 102(b) as being anticipated by Genbank data (Acc. No. M32681, June 1990). The human platelet glycoprotein polynucleotide contains a segment that is identical to at least 10 contiguous bases of SEQ ID NO:1 (see attached sequence comparison). The disclosed polynucleotide would hybridize to the mouse kappa opioid receptor (SEQ ID NO:1)

polynucleotide under low stringency conditions. In the absence of evidence to the contrary, claim 5 is anticipated by Genbank data.

7. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-5 and 9-14 are rejected under 35 U.S.C. § 103 as being unpatentable over Loh et al. in view of Schofield et al. and Sambrook et al.

Loh et al. review the biological role of opioid ant their receptors (page 138-142) and teach the presence of kappa opioid receptor in human placenta and human brain and other mammalian tissues (pages 123 and 124). Loh et al. also discuss methods for isolating the kappa receptor (pages 125-132, especially page 127). It appears that the kappa receptor can be purified

sufficiently for obtaining a partial amino acid sequence. However, Loh et al. do not teach isolation of the polynucleotide encoding the kappa receptor.

Schofield et al. teach isolation of a cDNA clone encoding the bovine opioid receptor by screening a bovine brain cDNA library with degenerate oligonucleotide probes corresponding to a partial amino acid sequence of the opioid receptor (page 489).

Sambrook et al. provide methods for expressing an isolated cDNA in host cells which are applicable to the expression of an opioid cDNA.

Since Loh et al. provide a method for purifying the kappa protein and disclose the source of the human kappa receptor and Schofield et al. teach how to obtain a partial amino acid sequence of the purified protein and how to generate oligonucleotide probes corresponding to the partial sequence for screening a cDNA library, one would have expected to be able to isolate the cDNA clone encoding the kappa receptor. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to isolate the cDNA encoding the human kappa receptor of Loh et al. by following the method of Schofield and by using oligonucleotide probes based on a partial amino acid sequence of the kappa receptor to screen a human placenta or brain cDNA library, so that one would be able to obtain large quantities of the receptor by expressing the

isolated DNA in host cells, as taught by Sambrook et al. It would also have been obvious to transfect the isolated DNA in other host cells such as PC12 or CHO-G44 for expression of the protein. PC12 and CHO-G44 are routinely used by the skilled artisan to express proteins. The motivation to isolate the receptor is provided by Loh et al. whose teachings are discussed above.

Thus, the claims are prima facie obvious over the prior art.

8. Claims 1-5 and 9-14 are rejected under 35 U.S.C. § 103 as being unpatentable over Loh et al. in view of Goldstein et al. and Sims et al.

The teachings of Loh et al. are as previously discussed. However, Loh et al. do not teach isolation of the polynucleotide encoding the kappa opioid receptor.

Goldstein et al. disclose a synthetic ligand that binds to kappa receptors with high affinity.

Sims et al. utilize a direct expression strategy to clone the IL-1 receptor from mouse T-cells. The method of Sims et al. comprises isolating mRNA encoding the receptor, obtaining the encoding cDNA using the isolated mRNA as the template, transfecting COS cells with the encoding cDNA, and screening the transfected COS cell for the ability to bind isotope-labelled IL-

1α (figure 1). The method disclosed by Sims et al. can be used to isolate other receptors with high affinity ligands.

Since Loh et al. reveal the source of the kappa receptor mRNA for making cDNA, Goldstein et al. disclose the ligand for the kappa receptor, and Sims et al. provide a method for isolating a receptor using its mRNA and its ligand , one would have expected to be able to successfully isolate the cDNA clone encoding the kappa receptor using the successfully established similar processes for receptors. Accordingly it would have been obvious to one of ordinary skill in the art at the time the invention was made to isolate the cDNA clone encoding the kappa receptor of Loh et al. by modifying the expression cloning method of Sims et al. and by using ^{125}I-dynorphin A of Goldstein et al. as the probe to screen COS cells transfected with cDNA encoding the human kappa receptor so that one would be able to express the isolated clone in host cells to obtain large quantities of the receptor for binding studies. It would also have been obvious to transfect the isolated DNA in other host cells such as PC12 or CHO-G44 for expression of the protein. PC12 and CHO-G44 are routinely used by the skilled artisan to express proteins. The motivation for isolating the DNA encoding the Kappa opioid receptor is provided by Loh et al. whose teachings are discussed above.

Thus, the claims are prima facie obvious over the prior art.

9. Claims 1-5, 9-11, 13, and 14 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-5 and 9-13 of copending application Serial No. 08/100,694. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

10. Claims 1-5 and 9-14 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 and 11-15 of copending application Serial No. 08/066,296. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application encompass the polynucleotides encoding the kappa receptor of the present application, and are co-extensive

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claim 12 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 11 of copending application Serial No. 08/100,694. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 11

of the copending application encompass the recombinant host cells of the present application.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel*, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

12. Claims 1-5 and 9-14 are directed to an invention not patentably distinct from claims 1-6 and 11-15 of commonly assigned copending application Serial No. 08/066,296.

The claims of the copending application encompass the polynucleotides encoding the kappa receptor of the present application.

Commonly assigned copending application Serial No. 08/066,296, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the

time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

13. No claim is allowed.

14. The oath or declaration is defective. A new oath or declaration in compliance with 37 C.F.R. § 1.67(a) identifying this application by its Serial Number and filing date is required. See M.P.E.P. §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not state that the person making the oath or declaration in a continuation-in-part application filed under the conditions specified in 35 U.S.C. § 120 which discloses and claims subject matter in addition to that disclosed in the prior copending application, acknowledges the duty to disclose material information as defined in 37 C.F.R. § 1.56(a) which occurred between the filing date of the prior application and the national

or PCT international filing date of the continuation-in-part application.

Any inquiry concerning this communication should be directed to Sally Teng, Ph.D., at telephone number (703) 308-4230.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4227.

Sally Teng
May 25, 1994

GARNETTE D. DRAPER
PRIMARY EXAMINER
ART UNIT 186